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BUCHANAN, INGERSOLL & ROONEY PC
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
10/17/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com
debra.hawkins@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/500,118	SEMB ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 22-65* is/are pending in the application.

4a) Of the above claim(s) *22-34 and 36-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20, 35, 57-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/12/07;8/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Arguments and Response, filed 7/12/07, have been entered. Claim 21 is cancelled; claims 1-20, 22-65 are pending; claims 22-34, 36-56 are withdrawn; claims 62-65 are newly added; claims 1-4, 6-11, 13, 14, 16, 17-20, 57-61 are amended; claims 1-20, 35, 57-65 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-21, 35, 57-61) in the reply filed on 1/12/07 is acknowledged.

Claims 22-34, 36-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/12/07.

Information Disclosure Statement

Applicants' Information Disclosure Statements, filed 7/12/07 and 8/28/07, have been considered.

Sequence Compliance

Applicants' submission of the substitute CRF, paper copy and appropriate statement has been accepted. This case is now sequence compliant.

Claim Objections

The prior objection of claim 17 is withdrawn in view of Applicants' amendment to the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20, 35, 57-65 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for obtaining pluripotent human blastocyst-derived stem cell lines, wherein the inner cell mass cells are co-cultured on fibroblast feeder cells, and the blastocyst-derived stem cell line is propagated on fibroblast feeder cells does not reasonably provide enablement for culturing inner cell mass cells or blastocyst-derived stem cell lines on any type of feeder cell layer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 2/12/07.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that a person of ordinary skill in the art would have reasonably predicted that additional feeder cells within the scope of the claims are likely to be effective in propagating pluripotent human blastocyst-derived stem cell lines. Applicants cite Lee to show that human uterine endometrial cells can be used as feeder cells in the establishment of culture of human ES cells, and additionally cite Ellerstrom *et al.* (see pages 15-16 of the Response).

Response to Arguments. Applicants' arguments have been considered, but are not persuasive. Applicants are reminded that the invention must be enabled at the time of filing.

MPEP 2164.05 states, "To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing.."

Both pieces of art cited by Applicants' are post-filing art,that do not overcome the prior rejection of record. Additionally, Ellerstrom teach culturing hESCs with human foreskin fibroblast feeders. See Abstract. Thus, Ellerstrom support the Examiner's scope of enablement, with regard to fibroblast feeders as a requirement for propagation of blastocyst-derived stem cell lines. Lee is not persuasive, because they teach different culture conditions than that which is instantly claimed. In particular, Lee teach culturing human embryonic stem cell lines under serum-free conditions, with feeder cells that are derived from uterine endometrium. Additionally, Lee show that it is not predictable to culture hES cells with any type of endometrial cell, stating that, "Richards and colleagues attempted to use hUECs as feeder cells to support the growth of hES cells and reported that adult glandular endometrium and adult stromal endometrium cannot maintain hES cells in an undifferentiated state." See page 48, 1st col., 2nd ¶.

Thus, given that the pieces of art that Applicants cite to rebut the Examiner's rejection support using fibroblast feeders (Ellerstrom) or support the unpredictability in the art with regard to culturing human ES cells in an undifferentiated state (Lee), and further, in view of the cited art of record (Thomson (1995), Thomson (2000), Lim (2002), who clearly show that the state of the art found it unpredictable that any type of feeder cell, for the breadth claimed, would be sufficient to support undifferentiated growth, it would not be predictable that any feeder cell type, when used as claimed, would maintain the human blastocyst-derived stem cells in an undifferentiated state.

Accordingly, in view of the teachings of the state of the art with regard to the culturing of human embryonic stem cells, the lack of direction or guidance provided by the specification for culturing the undifferentiated human blastocyst-derived stem cells with any type of feeder cell, in order to maintain the hES cells in an undifferentiated state, it would have required undue experimentation for one of skill in the art to carry out the claimed methods.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1-4, under 112, 2nd paragraph is withdrawn in view of Applicants' amendment, which now recite producing human blastocyst-derived stem cells from human oocytes and human blastocysts.

The prior rejection of claims 9, 60 and 61 under 112, 2nd paragraph, is withdrawn in view of Applicants' amendment, the claims no longer recite the term "about".

The prior rejection of claim 9, is withdrawn, in view of Applicants' amendments, which clarifies the language to a stem cell line.

The prior rejections of claim 9, 11, 14, 18 are withdrdawn in view of Applicants' amendments to the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21, 35, 57-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 102

The prior rejection of claim 21 under 35 U.S.C. 102(b) as being anticipated by Thomson *et al.* (Science, 282: 1145-1147) is rendered moot in view of Applicants cancellation of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-7, 12, 13, 16-20, 57-59 and newly added claims 62, 63 and 65 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with Thomson (1998) as evidenced by Stem Information (National Institutes of Health), when taken with Rijnders *et al.* and in further view of Lanzendorf *et al.*

Applicants' Arguments. Applicants argue that Thomson (2001) discuss producing primate ES cells, but only exemplifies producing an ES cell line from the Rhesus Macaque Monkey. Thus, Applicants conclude that this reference does not provide evidence to show the establishment of pluripotent blastocyst-derived stem cell lines, and one of ordinary skill would not have reasonably predicted that a method established for isolating and maintaining a culture of pluripotent blastocyst-derived stem cells from one species would succeed when transferred to another species. See page 18.

Applicants argue that the WO 99 27076 search report indicates that it is not straightforward to extrapolate the procedure for establishing ES cell lines in mice to a procedure for establishing ES cells in rats, despite the fact that mice and rats are evolutionarily closely related. Accordingly, Applicants argue that establishing a pluripotent human blastocyst derived stem cell line would not be obvious from the teaching of the preparation of ES cells from the Rhesus monkey. Applicants argue that methods for deriving ES cells from mice were known since 1981, but other species (such as pigs) were much later, which indicates that methods for isolating and culture murine blastocyst-derived stem cell lines were not easily transferable from one species to another. See page 18-19, last ¶.

Response to Arguments. These arguments have been considered but are not persuasive. MPEP §716.07 states:

> **Since every patent is presumed valid** (35 U.S.C. 282), **and since that presumption includes the presumption of operability** *(Metropolitan Eng. Co. v. Coe*, 78 F.2d 199, 25 USPQ 216 (D.C.Cir. 1935),**examiners should not express any opinion on the operability of a patent**. Affidavits or declarations attacking the

> operability of a patent cited as a reference must rebut the presumption of operability by a preponderance of the evidence. *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). (*Emphasis Added*)
>
> Further, since in a patent it is presumed that a process if used by one skilled in the art will produce the product or result described therein, such presumption is not overcome by a mere showing that it is possible to operate within the disclosure without obtaining the alleged product. *In re Weber*, 405 F.2d 1403, 160 USPQ 549 (CCPA 1969). It is to be presumed also that skilled workers would as a matter of course, if they do not immediately obtain desired results, make certain experiments and adaptations, within the skill of the competent worker. The failures of experimenters who have no interest in succeeding should not be accorded great weight. *In re Michalek*, 162 F.2d 229, 74 USPQ 107 (CCPA 1947); *In re Reid*, 179 F.2d 998, 84 USPQ 478 (CCPA 1950). (*Emphasis Added*).

Thomson (2001) teaches methods for isolation of pluripotent stem cells, including human ES cells. The claims to Thomson (2001) are directed to human ES cells. Applicants have not provide any affidavit or declaration that asserts that the Thomson (2001) patent is inoperative. This is not persuasive. The arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01.

MPEP §716.07 further states that:

> Where the affidavit or declaration presented asserts that the reference relied upon is inoperative, the claims represented by applicant must distinguish from the alleged inoperative reference disclosure. *In re Crosby*, 157 F.2d 198, 71 USPQ 73 (CCPA 1946). See also *In re Epstein*, 32 F.3d 1559, 31 USPQ2d 1817 (Fed. Cir. 1994) (lack of diagrams, flow charts, and other details in the prior art references did not render them nonenabling in view of the fact that applicant's own specification failed to provide such detailed information, and that one skilled in the art would have known how to implement the features of the references).

Thomson (2001) provide sufficient guidance, with regard to the isolation of human ES cells from human blastocysts to produce blastocyst-derived stem cell lines. This is further supported by Thomson (1998), who also specifically teach the production of human ES cells from human embryos. See prior Office action. Applicants' arguments are not within the scope of the claims. The Examiner has provided specific teachings that show the isolation of primate and human ES cells. These teachings are not utilizing murine techniques to isolate human ES cells. Thus, Thomson (2001) is proper and maintained.

Applicants' Arguments. Applicants further argue that the isolation of the ICM cells, according to the claimed invention is performed by mechanical dissection, without the use of enzymes and/or antibodies. Applicants argue that Thomson (2001) fails to teach or suggest utilizing mechanical dissection because they teach using a micropipette. Thus, Applicants' argue, given the delicacy and unpredictability of obtaining pluripotent stem cell lines from blastocysts, would not modified Thomson's methods to dissociate ICM-derived cells using mechanical dissection. See page 19 of the Response.

Applicants argue that the art of Rinjders and Lazendorf do not remedy the deficiencies of Thomson (2001) and Thomson (1998), because Rinjders teaches the predictive value of embryo morphology at a relative early stage for blastocyst formation, and Lazendorf teaches the selection of Grade 1 or 2 blastocysts. Applicants argue that both references teach using immunosurgery, but not mechanical dissection (see pages 19-20 of the Response). Applicants teaches that the term "mechanical dissection" is known to those in the art, and particularly because the cited art teaches pipetting, which is not mechanical dissection. See page 20, 1st full ¶.

Response To Arguments. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references

individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Although Thomson (2001) and Thomson (1998) do not specifically teach mechanical dissection of ICM cells (as recited in step iii) of claim 1, for example, Lazendorf discuss teach mechanical disassociation for replating of the cells (p. 134, 2nd col., 1st full ¶). This fulfills the limitation of the claims, because the claims require culturing the blastocyst on feeder cells to establish colonies and then disassociation of the cells using mechanical dissection, which is exactly what Lazendorf teaches. The claims, as written, require the mechanical dissection after culture of the ICM cells. Thus, it would have been obvious to one of ordinary skill in the art, to utilize mechanical dissection in order to isolate inner cell mass cells because this is a technique that was part of the ordinary capabilities of a person of ordinary skill in the art.

Applicants' Arguments. Applicants argue that the citation of the NIH stem cell information, provides no evidence that the H9 stem cell line is stable for more than 8 months (32 passages), as stated in Thomson (1998). Applicants argue that no karyotypes, stem cell specific immunomarkers, or pluripotency has been shown. Applicants argue that karyotypic aberrations are commonly observed when stem cells have been passaged enzymatically or chemically, and that, Applicants conclude, it would be likely that the H9 cell line carries an abnormal phenotype. See page 20, 2nd full ¶. Applicants argue that in contrast to the procedure taught by Thomson (1998), the present method enables the establishment of large numbers of stable pluripotent human ES cell lines. Applicants' state that the claimed method produces large numbers of culture units of ES cells. See pages 20-21.

Response to Arguments. These arguments have been considered but are not persuasive. This is not persuasive. The arguments of counsel cannot take the place

of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01.

Applicants have not provided an appropriate affidavit or declaration supporting that the H9 cell line carries an abnormal phenotype. Additionally, all that the claims require is that the cells have a proliferation capacity in an undifferentiated state for more than 21 months (claim 20, part i). The NIH's citation shows that this cell line has this proliferation capacity. Thomson (1998) show the other characteristics that are required of the cell line. Thus, Thomson (1998) in view of the NIH citation fulfill these limitations.

Additionally, if Applicants' feel that the claimed method results in an unexpected result then the claims should be commensurate in scope with that which is unexpected. See MPEP §716.02(d) which states, "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support."

Additionally, §716.01 (c) states that,

> "Objective evidence which must be factually supported by an ***appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art***, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence." "[A]ppellants have not presented any experimental data showing that prior heat-shrinkable articles split. Due to the absence of tests comparing appellant's heat shrinkable articles with those of the closest prior art, we conclude that appellant's assertions of unexpected results constitute mere argument."). See also *In re Lindner*, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); *Ex parte George*, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991). (Emphasis added).

Accordingly, it would have been obvious for one of ordinary skill in the art, to combine the teachings of Thomson (2001), Thomson (1998), who teach the production of human ES cell lines from human blastocysts, with the teachings of Rijnders and Lazendorf, with a reasonable expectation of success. One of ordinary skill would have been motivated to use the method of identifying fertilized oocytes/embryos of Grade 1 or 2, as taught by Rinjnders to increase the number of embryos that are capable of producing blastocysts. One of skill ordinary skill in the art would have been also motivated to use the methods, taught by Lazendorf *et al.* to identify blastocysts of Grade A or B, in order identify cells which have clearly defined inner cell masses, which would increase the probability of producing a successful ES cell line.

Claims 4, 8-10, 60 and 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with 'Thomson (1998) when taken with Rijnders *et al.* and in further view of Lanzendorf *et al.* as applied to claims 1-3, 5-7, 12, 13, 16-20, 57-59 and newly added claims 62, 63 and 65 above, and further in view of Marshall *et al.* (**Methods in Molecular Biology**: *Isolation and Maintenance of Primate Embryonic Stem Cells* 158: 11-18, January 2001).

Applicants' arguments, with regard to the non-obviousness of Thomson (2001)) when taken with 'Thomson (1998) when taken with Rijnders *et al.* and in further view of Lanzendorf *et al.* (see page 21 of the Response) has been addressed above.

Applicants' arguments regarding Marshall, which are similar to those of Thomson (2001) are not persuasive. In particular, the examiner notes that the operability of Thomson (2001) has been addressed above. Furthermore Thomson (2001) provides specific teachings for methods to produce human ES cells using techniques for Rhesus monkey ES cell isolation. Thomson (1998) show the production of human ES cells using these methods. Thus, it would be obvious for

one of ordinary skill in the art to apply the teachings of Marshall, particularly, with regard to the amounts of feeder cells used, because this technique was recognized as part of the ordinary capabilities of one skilled in the art.

Accordingly, given the combined teachings of Thomson (2001), Thomson (1998); Rijnders, Lazendorf and Marshall, it would have been obvious for one of skill in the art to utilize the methods to produce blastocyst-derived stem cell lines, and passage the cells every 4-5 days, at a density of 50,000 cells/cm^2, as taught by Marshall, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to utilize this amount of cells, as Marshall provide a specific protocol to maintain primate ES cells, and they state that because primate ES cells require "regular and meticulous attention to detail in all aspects of the culture process", one of skill in the art would turn to their protocol for direction and specific guidance with regard to the culture of primate ES cells. See page 12, 1st ¶.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 11 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with Thomson (1998) when taken with Rijnders *et al.* and in further view of Lanzendorf *et al.* as applied to claims 1-3, 5-7, 12, 13, 16-20, 57-59 and newly added claims 62, 63 and 65 above, and further in view of Conner.

Applicants' arguments on page 22, with regard to Thomson (2001) have been addressed above. In particular, the Examiner notes that the operability of Thomson (2001) has been addressed above. Furthermore Thomson (2001) provides specific teachings for methods to produce human ES cells using techniques for Rhesus monkey ES cell isolation. Thomson (1998) show the production of human ES cells using these methods.

Additionally, Applicants argue that although Conner may provide guidance on the use of MEF cells, and suggest that early passage of cells may be used for ES cell growth, the reference does not show this is the case for human blastocyst-derived stem cell lines. Applicants argue that given that methodologies are not readily transferable from one species to the next, Applicants argue that the claimed invention is not rendered obvious. See pages 22-23.

These arguments are not persuasive. One of skill in the art would be readily appraised the MEFs successfully maintain human ES cells in an undifferentiated state (see Thomson (2001), Thomson (1998)) for example. Thus, given that Conner teach utilizing MEFs for maintaining human stem cells, one of skill in the art would reasonably conclude that utilizing the methods of Conner, there would be a reasonable expectation of success, with regard to utilizing the MEFs in an early passage. One of ordinary skill in the art would have been sufficiently motivated to use early passage embryonic fibroblasts, because Conner clearly teach that later passage cells lose the ability to divide, and can have changes in characteristics that are not conducive to ES cell growth. Although Conner do not specifically teach that the cells should be passaged less than 3 times, this would be well-within the knowledge of the skilled artisan that the less passages the embryonic fibroblasts are subjected to, the more conducive the feeder cells would be to maintain ES cells. Thus, using feeder cells that have been passaged less than 3 times would be well-within the skills of the ordinary artisan. Additionally, because Conner suggest that the MEFs should be frozen prior to use, this provides additional motivation and suggestion that the embryonic fibroblasts should not be subjected to many passages.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 14-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with Thomson (1998) when taken with Rijnders *et*

al. and in further view of Lanzendorf *et al.* as applied to claims 1-3, 5-7, 12, 13, 16-20, 57-59 and newly added claims 62, 63 and 65 above, and in further view of Gardner *et al.* (1998), when taken with Gardner (1999).

Applicants' arguments are directed to Thomson (2001), which the Examiner has addressed above (see page 23 of the Response). These arguments have not been found persuasive. Thus, the rejection is maintained.

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to modify the methods of Thomson (2001), Thomson (1998), Rijnders and Lanzendorf, by culturing either the blastocyst of step ii) or the ICM cells of step iv) in a culture medium that contained hyaluronic acid, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification, as Gardner and Gardner (1999) provide guidance to show that culture medium that contains hyaluronic acid increases attachment of the blastocyst.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 35 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (U.S. Pat. No., 6,200,806 B1, issued March 13, 2001, cited above) when taken with Stratagene Catalog, 1988, p. 39.

Applicants' arguments are directed to Thomson (2001), which the Examiner has addressed above (see page23 of the Response). These arguments have not been found persuasive. Thus, the rejection is maintained.

Accordingly, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Thomson into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been

assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with Thomson (1998) when taken with Rijnders *et al.* and in further view of Lanzendorf *et al.* as applied to claims 1-3, 5-7, 12, 13, 16-20, 57-59 and newly added claims 62, 63 and and further in view of Xu *et al.* (Pub. No. US 2002/0072117 A1, published June 13, 2002). This is a new ground of rejection, necessitated by Applicants' amendments to the claims.

Thomson (2001), Thomson (1998), Rijnders and Lazendorf are described above. They do not specifically teach culturing the human blastocyst and ICM cells with human embryonic fibroblasts. However, prior to the filing of the claimed invention, Xu teach the production of human feeder cells that can be used to culture human ES cells. They teach producing human feeder cell line (¶ 17, Example 7 and claims), and culturing undifferentiated ES cells on human fibroblast feeder cells (Example 10).

Accordingly, it would have been obvious to one of ordinary skill in the art to modify the culture techniques taught by Thomson (2001) and Thomson (1998), to

utilize human embryonic fibroblasts, such as those taught by Xu, with a reasonable expectation of success. One of ordinary skill would have been motivated to make this modification, as suggested by Xu, that "Availability of established cell lines supporting pPS cells obviates the need to repeated prepare primary feeder cultures to continue the culture. (¶38), and further "The cell lines of this invention facilitate producing pPS cells on a commercial scale." See ¶40.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Thaian N. Ton/
Primary Examiner
Art Unit 1632